

THE MANAGEMENT OF BIOFILM FORMATION AFTER HYALURONIC ACID GEL FILLER INJECTIONS: A REVIEW

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Abstract

Background and aim. One of the most popular procedures of facial fillers in recent years has become the use of hyaluronic acid (HA). However, this method may be associated with local side effects of different severity. Many of them are not due to allergies, as previously believed, but to the formation of biofilm. We review the current knowledge on biofilm after HA.

Methods. All pertinent full text papers retrieved from PubMed under search words: "biofilm", "hyaluronic acid", "dermal fillers", "hyaluronic acid complications" and "hyaluronic acid side effects" were analyzed; 29 of 60 articles were selected for analysis.

Results. Local infections were reported: 13 cases are attributable to the activation of the biofilm. Clinical evolution is generally mild. Therapy should avoid NSAID and is based on the administration of antibiotics, oral corticosteroids, or 5-Fluorouracil. Removal of HA with hyaluronidase has also been proposed.

Conclusions. The use of HA in cosmetic procedures might be accompanied by local adverse effects attributable to biofilm formation. This usually has a mild evolution, but in special cases requires specific therapy.

Keywords: hyaluronic acid, biofilm, complications, fillers.

Introduction

The hyaluronic acid (HA) became one of the most popular cosmetic procedures, after its approval by FDA in 2002. It is used for lip augmentation, scars treatment (including acne scars) [1], nasolabial, glabellar, marionette, neck [2] wrinkles or even in improving the presentation of atopic dermatitis [3]. HA itself is an important component of the connective tissue that decreases during the aging process. In its natural form, the injectable HA lasts only 24-48 hours, thus the cosmetic product has to be stabilized through biochemical modifications [4]. According to the American Society of Plastic Surgeons (ASPS), in 2012 two million procedures were performed using soft tissue fillers (85% of them using HA). This procedure presented an increase of 5% compared to the year 2011. This impressive number shows the importance for doctors to know both the benefits and the side effects entailed by cosmetic HA gel, and to increase the awareness of their patients on the potential risks of these injections [5,6].

There are several reports on the adverse events of

this procedure in the literature, although most of them are minor and temporary. However, some complications can be devastating [7]. The most common complications include hematoma, allergies, asymmetries, skin necrosis or infections [4].

A new concept considers that many HA complications are due to biofilms and not due to allergies or other inflammatory response. The biofilms are groups of microorganisms in which cells stick to each other in a three-dimensional structure, on a given surface. Usually the biofilm is covered by a polymeric substance which offers antibiotic resistance. The biofilms live in dormant state (low-grade infection), but an active infection can be triggered by trauma, hematogenic infection or iatrogenic manipulation. Because the biofilms are hard to culture and to detect, many HA complications were not correctly diagnosed and were attributed to allergies.

The aim of this paper is to review available evidence on the diagnosis and treatment of biofilm formation after HA filler injections.

Methods

A PubMed database search was performed; cosmetic

surgery books were also screened. The used keywords were “biofilm”, “hyaluronic acid”, “dermal fillers”, “hyaluronic acid complications” and “hyaluronic acid side effects”. The cited references of each article were searched, and those considered relevant were reviewed. A first “screening” included 60 articles from which 29 were selected. Nine different items were followed: etiology, pathophysiology, clinical presentation, diagnostic, differential diagnosis, prognosis, prevention and future directions.

The evidence was not large enough to undertake a systematic review of this issue.

Results

Local infections

The number of infections after HA dermal filler injections is very small. Only 13 cases that were considered a possible activation of an existing biofilm were found. The main symptoms consisted in swelling, induration, rash and granulomas [10-14]. These complications appeared between 2 days and 8 months after injection.

There was no microbiological culture that could determine an infective disease. There were two reports of IgE and IgG antibodies tests that showed negative [15,16].

The treatment of these infections consisted in antibiotherapy, oral corticosteroids, hyaluronidase or 5-Flourouracil [17,18].

Etiology and pathogenesis

The etiology of many HA gel injections for cosmetic facial augmentation remains a very debatable subject. Until recently, specialized papers and scientific publications have tried to find explanations for these events. Some have supported the theory of an allergy to the HA (highly unlikely from an immunological point of view), or that of an abscess (but no bacteria could ever be identified in the microbiological cultures).

A new concept, which is growing to be more widely accepted, is that of the bacterial biofilm that is created around the HA after injection. The biofilm is a complex three-dimensional structure of bacteria that creates an adhesive and protective matrix around a foreign body. As the biofilm progresses, it offers better protection against antibiotics to all constituent bacteria [19]. Typically, the biofilm lives in a passive state causing the so-called “low-grade infection” [20,21]. However, there are certain factors that can activate the biofilm (low immunity, dental infections, haemolytic contamination, etc.) resulting in an inflammatory response leading to abscess or systemic infections [14].

Clinical presentation

Complications after hyaluronic acid injection for cosmetic purposes are rare, but cause great inconvenience to patients. They are completely healthy people who resort to cosmetic procedures only to get an appearance closer to perfection. The results of the complications are difficult

to accept and cause great frustration to both patients and physicians. Fortunately, the majority of facial fillers complications are transient, but the infections can represent a total disaster in both patient aesthetic aspect and quality of life. The haematomas are the most common side effect and last between 2-5 days and are usually associated with the use of aspirin or NSAIDs [4].

The acute allergic reactions were demonstrated for the old products containing bovine collagen. Therefore allergy tests were recommended. With the newer products (cross-linked hyaluronic acid), an allergic reaction has no theoretical evidence. Instead the clinical presentation of what is supposed to be an allergic reaction fits perfect to the symptoms of infection: pain, redness, swelling, heat to the site or even pus or fistula [4,11,12,16]. When the complications were reported immediately (couple of days) after the procedure, an acute dermal contamination is to be considered. On the other hand when the symptoms appear late, even after months after the injection of HA, an activation of a dormant biofilm infection is to be considered [18]. In the patient history endodontic procedures, oral infections or cosmetic invasive treatments are often described, days before the onset of symptoms [14].

Diagnosis

Bacteria are among the most adaptive organisms. By continually evolving, they develop resistance to a wide range of antibiotics. A key factor of their resistance is their ability to form biofilms [22]. The biofilms are “aggregate of microorganisms in which cells that are frequently embedded within a self-produced matrix of extracellular polymeric substance adhere to each other and/or to a surface” (IUPAC definition). There are five steps in the biofilm formation: initial attachment, irreversible attachment, maturation I, maturation II and dispersion. Especially in the dispersion faze the biofilm is secreting a protective barrier consisting in carbohydrates [22]. This barrier is increasingly antibiotic resistant [23].

The identification of biofilms is difficult. Usually the microbiological cultures from a biofilm infected tissue are negative [18,22]. In the literature many methods were used to evidence biofilms including classic culture plates, the “tube method” or the Congo red agar test [24,25,26]. Some authors consider the in situ fluorescent hybridization (FISH), using peptide nucleic acid the most accurate method [18]. The HA is a non permanent filler but because in vivo persistence of 6-36 month was described [27], the bacteria have the needed time to organize in biofilms.

Treatment

The symptoms described above were empirically considered allergies or immune hypersensitivity reactions. The used treatment included steroids and NSAIDs as well as antihistamines. Not only do these treatments fail to help out, but they also complicate the situation locally.

Since nowadays it is accepted that those complications are due to activations of biofilm infections, the steroids and NSAIDs should be avoided. A successful therapeutic plan will include broad-spectrum antibiotics like ciprofloxacin, amoxicillin or clarithromycin up to six weeks [4,11,18].

Another important therapeutical measure is the use of hyaluronidase to remove the HA. Conform to the theory “no foreign substance, no biofilm” the lyses of the HA gel will destroy the mechanical support of the biofilm colony.

A study from 2009 presented the benefits of 5-Flouracil in biofilm reductions through inhibition of DNA synthesis in bacteria [28]. Dayan SH and al. use 5-FU administration for long term indurations after HA gel cosmetic filler complications [18]. A less used technique but with good long term results is the laser lyses in very resistant inflammatory reaction [29]. The most invasive method, which is to be used for the severe chases, is the surgical resection. This radical treatment offers the less cosmetic satisfaction in patients.

Prognosis

When the above suggested treatments are correctly applied the symptomatic is improved and the infection is cured. Unfortunately the aesthetic outcome after the recovery of an activated biofilm formation may be not very good accepted by the patients. It can leave facial asymmetry or contractile scars that need plastic surgery or dermatocosmetic interventions.

Prevention

To prevent a possible contamination of the HA gel, a very good skin disinfection is mandatory. The use of antiseptic solution (alcoholic or non alcoholic) are highly recommended. The injections through de oral mucosa as well as multiple injection sites are to be avoided.

The lack of sufficient data in the literature should encourage scientist to find an experimental model to explain the appearance of biofilms that cause erythema, inflammation and pain in some cases of injection of HA for cosmetic purposes. Also, improved protocol for the treatment of these complications should be developed according to evidence based medicine.

Conclusions

The HA gel injections for facial augmentation should not be considered a “semi-sterile procedure” anymore. The use of proper dermal antiseptic solution is essential. The so called allergic or hypersensitivity reactions are likely to be a microbial contamination. In these cases, the steroids and NSAIDs are to be avoided; instead, a broad spectrum antibiotherapy is useful. The use of hyaluronidase for HA removal, as well as 5-FU administration for biofilm reduction proved helpful.

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